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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,035	04/17/2001	Weichao G. Chen	PC10866AMGM	8768

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Gregg C. Benson
Pfizer Inc.
Patent Department, MS 4159
Eastern Point Road
Groton, CT 06340

EXAMINER
HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 11/26/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,035	CHEN ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of the IDS filed on 9-27-2002 has been entered.

2. Claims 1-29, 31 are pending. Claim 30 has been canceled according to the amendment filed on 11-16-2001. These claims are subjected to the same rejections set forth in the previous office actions and are reiterated as follows.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-29, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamanaka (WO 99/43663, PTO-1449).

Hamanaka generically discloses a pyrazole-carbonyl guanidine compound for treating ischemia (claims 1, 102). A specific compound, [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine, is described (claim 103).

The instant compound differs from Hamanaka's compound in having an additional 2-hydroxy (which tautomerizes to 2-oxo) on the quinolinyl moiety.

Hamanaka, however, teaches that 2-hydroxy is an optional substituent among a small genus (claim 102, definition of R2).

At the time of the invention, one of ordinary skill in the art would be motivated to add the optional 2-hydroxy onto the quinolinyl of the [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine to arrive at the instant invention, with the reasonable expectation of obtaining an additional compound useful for treating ischemia, since Hamanaka had clearly taught that any species within the preferred genus would be effective in reducing tissue damage resulting from tissue ischemia. In the absence of unexpected results, choosing one among many is prima facie obvious to one of ordinary skill in the art.

The declaration under 37 CFR 1.132 filed on 11-16-2001 has been fully considered but is insufficient to overcome the rejection for the following reasons. Firstly, the measurement of the plasma half-life and the advantageous longer plasma half-life of the instant quinolone compound are not described in the specification. Secondly, the result is not unexpected in view of the disclosure that administration of the 5[-cyclopropyl-1-(quinolin-5-yl)-1-H-pyrazole-4-carbonyl]-guanidine (compound A) lead to the instant 5[-cyclopropyl-1-(quinolon-5-yl)-1-H-pyrazole-4-carbonyl]-guanidine (compound B) in vivo (admitted by the applicant in claim 30). Compound A is therefore a prodrug of compound B (claim 1, proviso) and one of ordinary skill would expect the precursor compound to have a shorter plasma half-life because it is being metabolized. Since unexpected results have not been established, the instant remains obvious over Hamanaka.

5. Claims 1-29, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamanaka (WO 99/43663, PTO-1449) in view of Munson and Beedham.

Hamanaka discloses the compound, [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine (claim 103).

The instant compound differs from Hamanaka's compound in having an additional 2-hydroxy (which tautomerizes to 2-oxo) on the quinolinyl moiety. The instant is therefore the oxidation metabolite of the prior art compound. The hydroxylation reaction is well-known in the pharmaceutical art as one of the phase I metabolic transformations of drugs (Munson, pages 54-55, Table 2.5). The oxidation of quinoline to 2-quinolone by an oxidase from the liver has been specifically described by Beedham (abstract). The prior art quinoline compound is therefore a prodrug of the instant quinolone compound and they are expected to share similar biological

activities. One of ordinary skill in the art would be motivated to make the active quinolone compound to arrive at the instant invention. To one of ordinary skill in the art, the instant metabolite compound is prima facie obvious over its prodrug (as admitted by the applicant in the proviso of the claims) in the absence of unexpected results.

Applicant argues that Munson does not specifically teaches the hydroxylation of the quinoline compound to arrive at the instant quinolone compound. Indeed Munson only generically teaches the hydroxylation reaction as one of the possible metabolic pathways in the body, but this text-book teaching serves to demonstrate that it is a well known metabolism. Furthermore, Beedham specifically teaches the oxidation of quinoline to 2-quinolone by an oxidase in the liver. Beedham's compound is not identical to but is similar to the instant quinolinyl compound, and one of ordinary skill in the art would expect the same oxidation reaction occurs in the instant quinolinyl compound. The Declaration fails to render the instant unobvious for reasons set forth in the preceding paragraph. In the absence of unexpected results, the instant remains obvious over the prior art of record.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-29, 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the corresponding claims of

copending Application No. 09/367731, the US equivalent of Hamanaka (WO 99/43663), which has been allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are encompassed by the copending claims, and for reasons set forth in paragraph 4 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-29, 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the corresponding claims of copending Application No. 09/367731 (the US equivalent of Hamanaka (WO 99/43663), which has been allowed) in view of Munson and Beedham. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth in paragraph 5 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

9. No claims are allowed.

10. This is a RCE wherein no amendment to the claims has been made. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Evelyn Huang
Primary Examiner
Art Unit 1625

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November 15, 2002